

# Minimal Clinically Important Improvement: The Rheumatologist's Perspective

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# Amount of Improvement

- Absolute and percent change from baseline in the treatment group
- Absolute difference between the treatment and control groups
- Effect size
  - Scale-free measure of the relative size of the effect of an intervention
  - Mean difference between groups / pooled SD
  - Cohen (1969): 0.2 (small), 0.5 (medium), 0.8 (large)

# “It’s good to be better”

- Minimal clinically important improvement
  - Minimal clinically important improvement (MCII) is the smallest outcome measure change important to patients.
- Minimal clinically important difference
  - A minimal clinically important difference (MCID) can be defined as the smallest difference in score on an outcome measure (e.g. pain, disability, quality of life) which patients perceive as beneficial.

# “It’s better to be good”

- Patient Acceptable Symptom State
  - Patient Acceptable Symptom State (PASS) has been defined as the highest level of symptom beyond which patients consider themselves well.

What are the clinically relevant outcomes in patients with OA from the rheumatologist's point of view?

# Outcome Measures for OA: The Rheumatologist's Perspective

- Visual Analog Scale (VAS) or Numerical Rating Scale (NRS)
- Western Ontario McMaster Osteoarthritis (WOMAC) Index
- Knee and Hip Osteoarthritis Outcome Score (KOOS and HOOS)
- OARSI-OMERACT Osteoarthritis Pain Measure (ICOAP)
- Lequesne Algofunctional Index
- Australian Canadian Osteoarthritis Index (AUSCAN) for hand OA

# REPORT Database

- Double-blind placebo-controlled randomized clinical trials in patients with hip or knee OA
  - Published before August 2009
  - Oral, topical or transdermal agents
- Responsiveness of measures assessed using treatment effect and standard effect size
- 125 RCTs provided data on at least one outcome domain

# Symptom Modifying Trials: 1<sup>ary</sup> Outcomes

- Pain intensity
  - WOMAC pain subscale or pain VAS/NRS
- Functional limitation
  - WOMAC function subscale or Lequesne index
- Patient global assessment
  - PGART superior to PGA

# Symptom Modifying Trials:

## 2<sup>ary</sup> Outcomes

- Percent of patients achieving a treatment threshold
  - OARSI/OMERACT Responder Index
  - Minimally Clinically Important Improvement
  - Patient Acceptable Symptom State
  - IMMPACT Recommendations
    - Moderate improvement  $\geq 30\%$  decrease
    - Substantial improvement  $\geq 50\%$  decrease

# OMERACT-OARSI Responder Index

High improvement in pain or function  $\geq 50\%$  and absolute change  $\geq 20$

↓ Yes  
**Responder**

↓ No

Improvement in  $\geq 2$  of the following 3

- Pain  $\geq 20\%$  with absolute change  $\geq 10$
- Function  $\geq 20\%$  and absolute change  $\geq 10$
- PGA  $\geq 20\%$  and absolute change  $\geq 10$

↓ Yes  
**Responder**

↓ No  
**Non-responder**

# Defining Clinically Relevant Improvement in Patients with Osteoarthritis of the Knee

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# Objective

- To validate the OMERACT-OARSI Responder Index
- Test the hypothesis that patients with knee OA participating in a clinical trial who fulfil the OMERACT-OARSI Responder Index will have better overall health status as measured by both arthritis-specific and general measures.

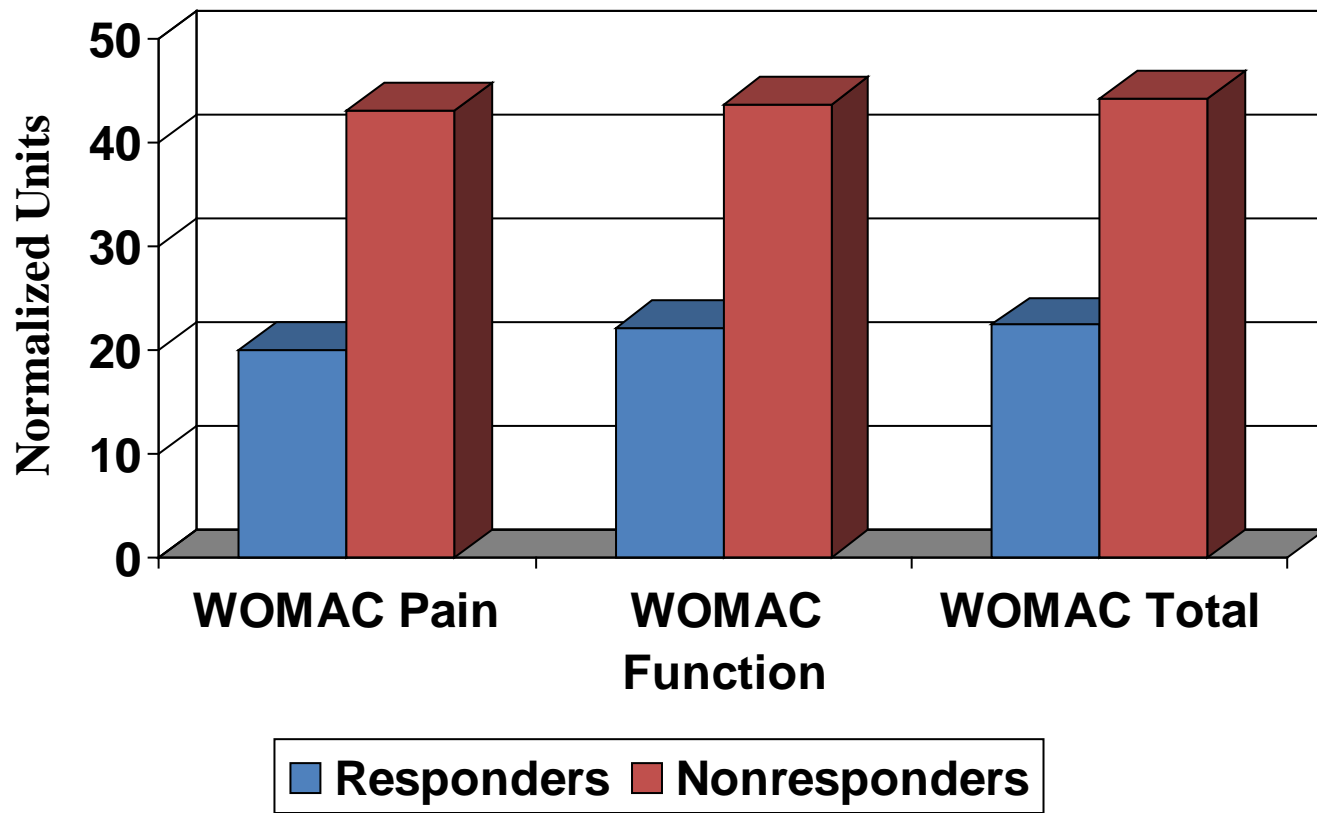
# Patient Cohort

- 570 patients with symptomatic knee OA enrolled in a randomized, 3-arm, 6-month, parallel group trial
  - Traditional Chinese acupuncture
  - “Sham” acupuncture
  - Education/attention control

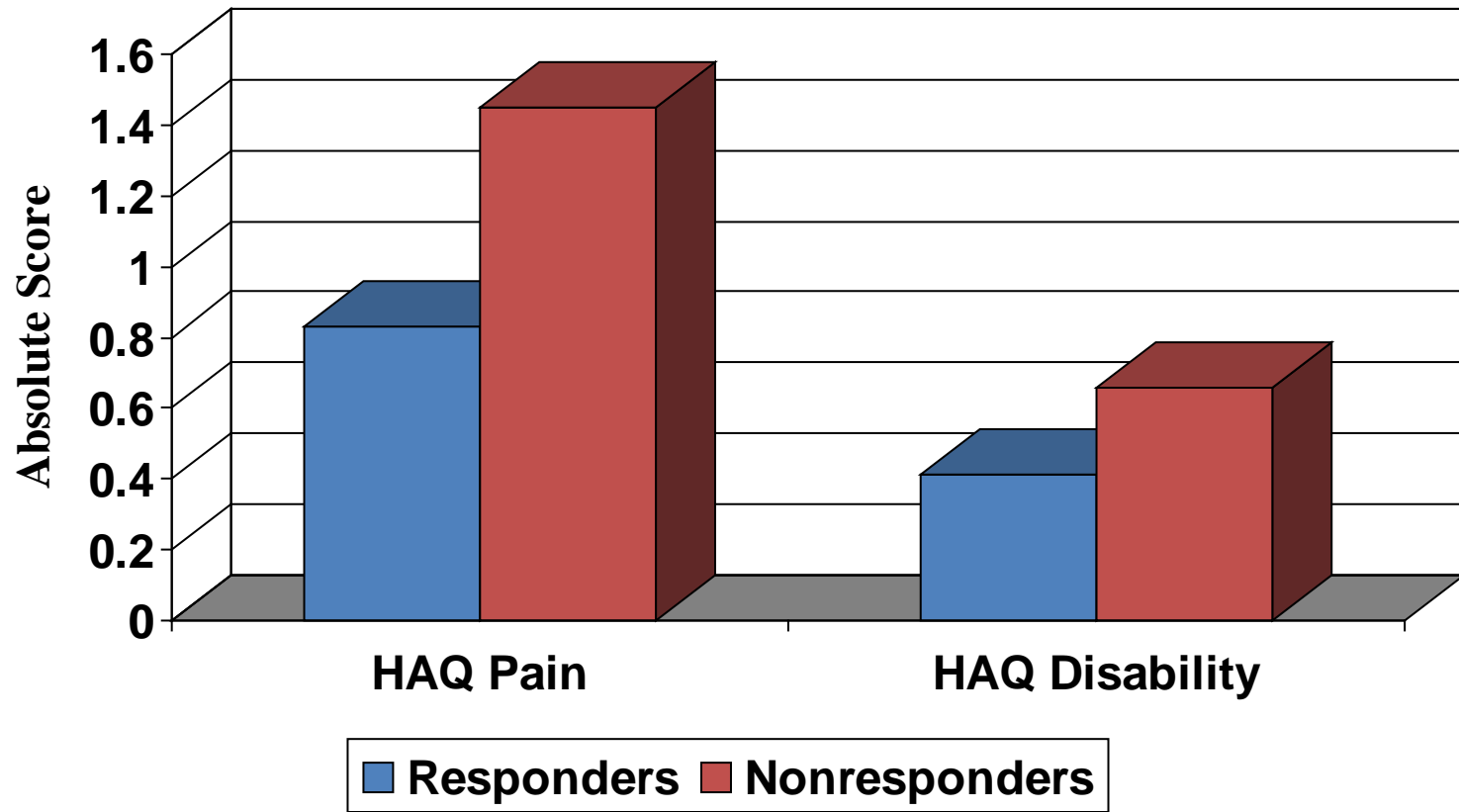
# Comparison of Outcomes by OMERACT-OARSI Response

- 236 (41.4%) of 570 patients randomized achieved an OMERACT-OARSI Response at the end of study
  - 61% of 386 completers

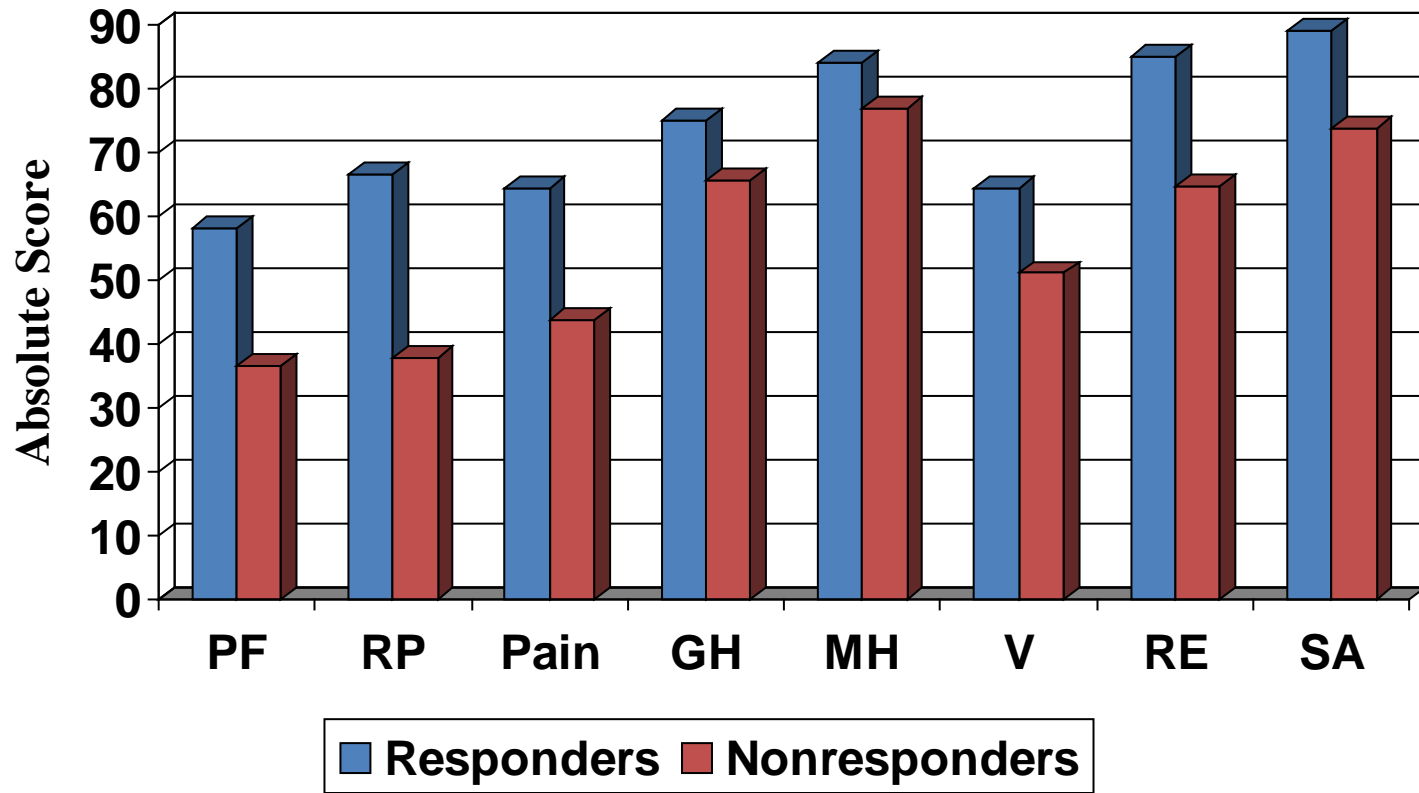
# WOMAC Scores by OMERACT-OARSI Response



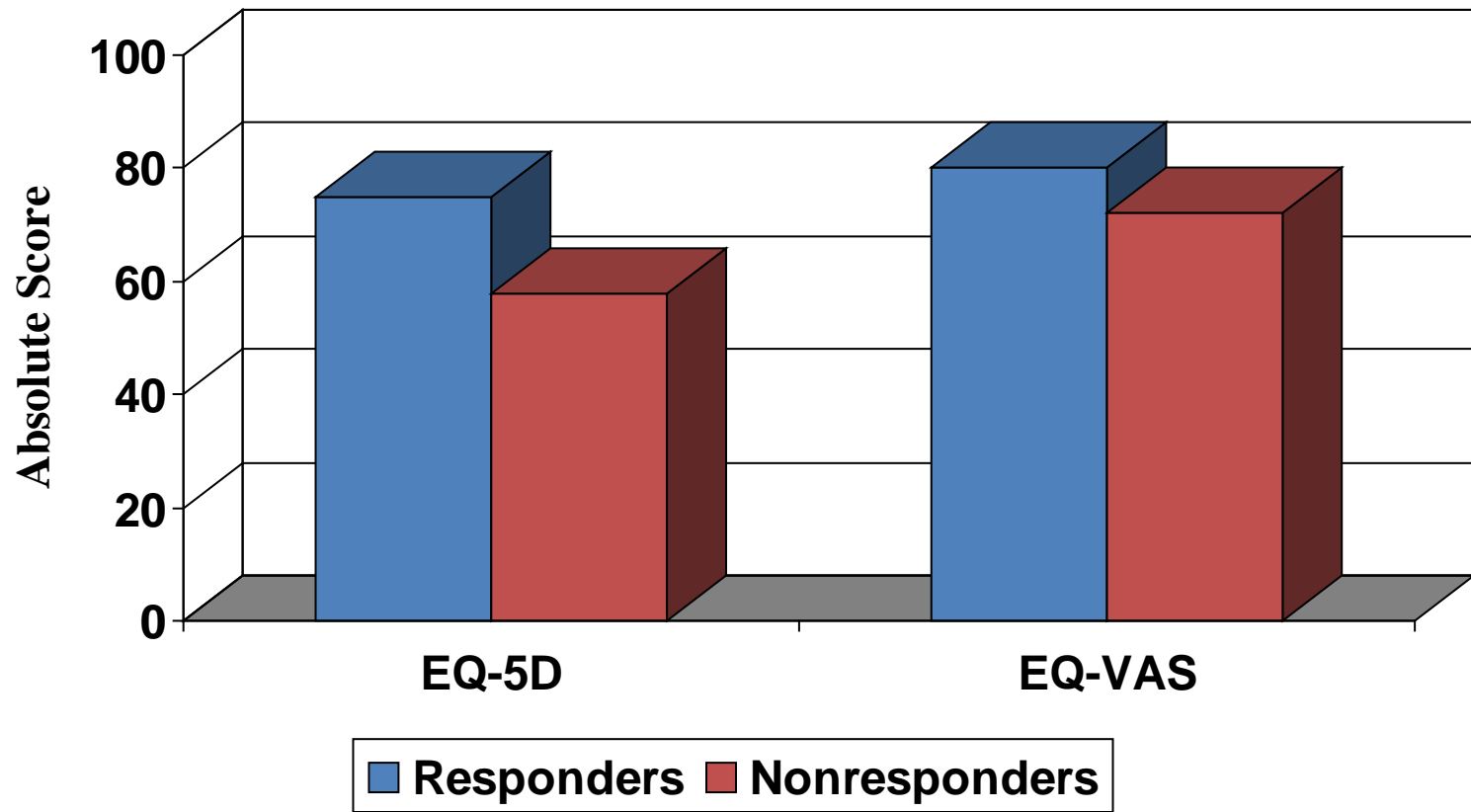
# HAQ Scores by OMERACT-OARSI Response



# SF-36 Scores by OMERACT-OARSI Response



# EuroQoL Scores by OMERACT-OARSI Response



# Minimal Clinically Important Improvement (MCII)

- Smallest change in a measurement that signifies an important improvement in a patient's symptoms
- 75%ile of distribution of change score among those who had good or excellent improvement with therapy
  - Pain in knee OA                      20 mm
  - Pain in hip OA                        15 mm

# Patient Acceptable Symptom State (PASS)

- Value in the measurement of a patient's symptom beyond which the patient considers herself well
- 75%ile of distribution of absolute score among those who are satisfied with their current state after therapy
  - Pain in Knee OA                      30 mm
  - Pain in Hip OA                        35 mm

# Objective

- To validate the MCII and PASS in patients with knee OA
- Test the hypothesis that patients who fulfil the OMERACT-OARSI Responder Index have increased odds of having MCII and PASS at the completion of the trial

# Data Analysis

- Post-hoc analysis using data from all 3 treatment groups combined
- Calculated proportion of patients with MCII and PASS
- Responders identified using OMERACT-OARSI Responder Index
- Odds ratios (95% CI) calculated
- Analyses conducted on ITT population using EpiCalc v2.0

# State Measures in OA Patients

- MCII
  - Pain 177 (31%)
  - Function 220 (39%)
  - Global 136 (24%)
- Highly significant associations between having an MCII on multiple domains

# State Measures in OA Patients

- PASS
  - Pain 241 (42%)
  - Function 221 (39%)
  - Global 177 (31%)
- Highly significant associations between being in a PASS on multiple domains

# State Measures in OA Patients

- Highly significant associations between achieving an OMERACT-OARSI Response and having either an MCII or a PASS for each of the 3 domains, especially pain and function.

# IMPACT Recommendations

- Provisional benchmarks for interpreting changes in chronic pain clinical trial outcome measures
- Pain intensity: 0-10 NRS
  - Moderately important improvement:  $\geq 30\%$
  - Substantial improvement:  $\geq 50\%$

# Duloxetine in Knee OA:

## Clinically Relevant OA Outcomes

- Post-hoc analysis of data from 2 placebo-controlled RCTs of duloxetine in knee OA
  - 487 patients; mean age 62 years, 70% women
- Treatment response assessed using validated OA responder outcomes
  - Agreement measured with K statistic

# Summary of OA Outcomes

Outcome measure	Duloxetine (%)	Placebo (%)	RR (95% CI)	NNT (95% CI)
OMERACT-OARSI	69.7	52.1	1.33 (1.15, 1.55)	6 (4, 12)
MCII Pain	51.8	33.3	1.55 (1.25, 1.93)	6 (4, 11)
MCII Function	65.3	49.4	1.32 (1.13, 1.55)	7 (5, 15)
PASS Pain	53.1	34.6	1.54 (1.24, 1.90)	6 (4, 11)
PASS Function	48.6	36.5	1.33 (1.07, 1.65)	9 (5, 32)
IMMPACT ≥30%	64.9	44.9	1.45 (1.22, 1.71)	5 (4, 9)
IMMPACT ≥50%	47.4	30.9	1.53 (1.21, 1.94)	7 (4, 13)

# REFLECT Study: Objective

- To estimate the Minimum Clinically Important Improvement (MCI) and Patient Acceptable Symptomatic State (PASS) values for 4 generic outcomes in 5 rheumatic diseases and 7 countries.

# Methods

- A multinational (Australia, France, Italy, Lebanon, Morocco, Spain, The Netherlands), 4-week cohort study involving 1,532 patients with ankylosing spondylitis, chronic back pain, hand osteoarthritis, hip and/or knee osteoarthritis or rheumatoid arthritis and NRS pain scores  $\geq 3$  who were prescribed NSAIDs.
- Generic and disease-specific patient reported outcomes (PROs) collected at baseline and follow-up visits.
- The MCII and PASS values were estimated with the 75<sup>th</sup> percentile approach for 4 generic outcomes: pain, patient global assessment, functional disability and physician global assessment, all normalized to a 0-100 score.

# External Anchor Questions: MCII

- Patients assessed the change from baseline on a 3-point Likert scale (improved, no change, or worse). If they reported an improvement, they were asked how important this improvement was to them (very important, moderately important, slightly important or not at all important).

# External Anchor Question: PASS

- Patients were asked “If you were to remain for the rest of your life as you were during the last 48 hours, would this be acceptable or unacceptable for you?” with a dichotomous response mode: acceptable or unacceptable.

# Results (1)

- 1532 patients enrolled
- 1505 (98%) patients completed
- 668 (44.5%) reported slight or moderate improvement
- 1014 (67.4%) reported being in an acceptable state

# MCII and PASS for Hip/Knee OA

- Analysis limited to 353 patients with hip or knee OA and 249 patients with hand OA
- WOMAC Pain:
  - MCII Absolute Change (95% CI) was 9 (6, 12).
  - MCII Relative % Change (95% CI) was 17 (12, 21).
  - PASS (95% CI) was 39 (36, 44).
- WOMAC Function:
  - MCII Absolute Change (95% CI) was 6 (3, 9).
  - MCII Relative % Change (95% CI) was 12 (7, 16).
  - PASS (95% CI) was 48 (45, 51).

# MCII and PASS for Hand OA

- AUSCAN Pain
  - The MCII (Absolute Change and 95% CI) was 8 (5, 10). The MCII (Relative % Change and 95% CI) was 15 (13, 17).
  - The PASS (95% CI) for AUSCAN pain was 41 (38, 45).
- AUSCAN Physical Function
  - The MCII (Absolute Change and 95% CI) was 4 (1, 6). The MCII (Relative % Change and 95% CI) was 8 (5, 11).
  - The PASS (95% CI) for AUSCAN physical function was 45 (41, 49).

# Thank you for your attention

